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Evaluation of corneal endothelial morphology in type 2 diabetes mellitus with specular microscopy

Corneal endothelium in type 2 diabetes mellitus

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Abstract
Aim: In this study, we aimed to evaluate the corneal endothelium using a specular microscopy in patients with type 2 diabetes mellitus (DM).
Material and Methods: The right eyes of 30 DM patients without any ocular findings, 30 DM patients with non-proliferative diabetic retinopathy (NPDR), and 30 DM patients with proliferative diabetic retinopathy (PDR) were evaluated in the study. Cell density (cells/mm2), corneal thickness (µ), hexagonal cell ratio (%), and coefficient of variation (cell area standard deviation/mean cell area, µm2) of the corneal endothelium of these patients were assessed with a specular microscope.
Results: There was no significant difference between the groups in terms of corneal thickness. While there was no significant difference between the control group and the group with NPDR in terms of endothelial cell density, hexagonality and coefficient of variation, a significant difference was found between the PDR group and both the control and NPDR groups.
Discussion: Since we found that disease progression leads to deterioration in corneal endothelial morphology in type 2 DM patients, we believe that it is important to try to prevent disease progression by controlling the blood glucose levels and using specular microscopy during follow-up and treatment in these patients.

Keywords
Type 2 Diabetes Mellitus, Specular Microscopy, Corneal Endothelium, Hexagonality, Coefficient of Variation

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Introduction

The corneal endothelium consists of a single non-renewable layer of predominantly hexagonal cells. Corneal endothelial cells keep the stroma dry by actively removing water, which is a vital function in maintaining normal corneal transparency [1]. The corneal tissue is avascular. Maintaining normal corneal metabolism depends on a critical oxygen level, below this level, a series of acute metabolic events, including an increase in stromal lactate, a decrease in intercellular pH, and an increase in corneal hydration may occur [2]. Oxygen required for basic metabolism of the cornea is primarily obtained from the atmosphere through tears and diffusion on the anterior surface of the cornea. The aqueous humor in the anterior chamber also supplies oxygen to the cornea [3].

Diabetes mellitus (DM) is a metabolic disorder resulting from a defect in insulin secretion, insulin action, or both. Insulin deficiency also causes chronic hyperglycemia by causing disorders in carbohydrate, fat and protein metabolism. As DM progresses, increasing tissue and vascular damage leads to serious diabetic complications such as retinopathy, nephropathy, and neuropathy [4,5].

DM is divided into two main groups as type 1 and type 2. Individuals with type 1 diabetes have little or no endogenous insulin secretory capacity and therefore require insulin therapy to survive [6]. Type 2 diabetes is the most common form of diabetes and is characterized by disorders in insulin secretion and insulin resistance [7]. Diabetes is seen in 5-7% of the world's population [8].

Specular microscopy (SM) is a non-invasive approach for the qualitative, quantitative and morphometric evaluation of corneal endothelial functions [9]. SM enables determination of corneal thickness, cell density (CD), which indicates the number of cells per mm2 of the corneal endothelium, pleomorphism, which indicates variation in cell shape in the endothelium, and polymegathism, which indicates variation in individual cell area. Pleomorphism shows the hexagonal cell ratio, and polymegathism shows the coefficient of variation, determined by the ratio of the cell area standard deviation to the mean cell area.

Diabetic retinopathy is angiopathy with involvement of retinal capillaries. Patients are divided into two groups as non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR). Microaneurysms, soft and hard exudates, intraretinal microvascular abnormalities are seen in NPDR. If neovascularization, vitreous hemorrhage, tractional retinal detachment and macular edema are detected, the disease is classified as PDR [10].

Corneal cells have a very limited mitotic capacity. Therefore, when cell loss occurs, adjacent cells expand and shift to maintain endothelial continuity. This causes an increase in polymegathism and pleomorphism [1]. Cell loss and endothelin status can be more precisely determined based on the assessment of polymegathism and pleomorphism.

Diabetic patients are susceptible to corneal epithelial disorders such as superficial punctate keratopathy and epithelial erosion [11]. In addition, permanent epithelial defects and recurrent erosions may occur in the corneal epithelium during vitreoretinal surgery and photocoagulation [12]. This shows that the cornea is more sensitive to pathologies in diabetic patients. Our aim in this study was to evaluate corneal endothelial morphology using specular microscopy in patients with type 2 diabetes.

Material and Methods

This cross-sectional prospective study was conducted in our hospital's ophthalmology outpatient clinic between January 2020 and January 2021. Before the initiation of the study, informed consent was obtained from the patients and ethical committee approval was obtained from the Ethics Committee of our hospital. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

All patients underwent a complete and detailed ophthalmologic evaluation, including best-corrected visual acuity, slit lamp biomicroscopy, Goldmann applanation tonometry, intraocular pressure measurement (IOP), pachymetry, triple-mirror contact lens gonioscopy, and fundoscopy. Afterwards, right eyes of all patients were photographed with specular microscopy (Specular Microscope CEM-530, NIDEK). Cell density (CD), hexagonal cell ratio (HEX), corneal thickness (CT) and coefficient of variation (CV) in the corneal endothelium were assessed from the SM images.

Patients with glaucoma, uveitis, retinal disease, hypertensive retinopathy, epiretinal membrane and retinal detachment, corneal disease, pseudoexfoliation syndrome, high myopia and hyperopia (>6D), corneal opacity, patients who could not cooperate during SM, those with a history of ocular trauma and surgery, and those who used eye drops and contact lenses were excluded from the study. In addition, patients with dementia, Parkinson's disease, epilepsy, vascular disease, and psychiatric disease were excluded from the study.

Statistical analysis was performed using the SPSS® 22.0 (Statistical Package for Social Sciences, IBM Inc., Chicago, IL, USA) package program. The variables were investigated using analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk's test) to determine if they were normally distributed. Descriptive analyses were presented using means and standard deviations for normally distributed variables and median and interquartile range for the non-normally distributed and ordinal variables. One way ANOVA was used to compare normally distributed variables and Levene's test was used to assess the homogeneity of the variances. Kruskal-Wallis tests were conducted to compare non-normally distributed variables. An overall p-value of less than 0.05 was considered statistically significant.

Results

The right eyes of 30 DM patients without any ocular findings, 30 DM patients with NPDR, and 30 DM patients with PDR were evaluated. Socio-demographic characteristics of the patients are shown in Table 1.

We evaluated corneal thickness (μ), endothelial cell density (cells/mm2), hexagonal cell ratio in endothelium (%) and coefficient of variation (μm2) in all patients using SM. We determined that there was a significant difference between the PDR group and both the NPDR and control groups in terms of

CD, HEX and CV. However, no significant difference was found between the NPDR group and the healthy control group. No significant difference was found between the three groups in terms of CT. The data are summarized in Table 2.

Table 1. Socio-demographic results of groups

Parameter	Control Group (n=30)	NPDR Group (n=30)	PDR Group (n=30)	p value
Sex (F/M)	14/16	13/17	14/16	
Age	50.26±12.18	50.20±11.82	50.83±12.58	0.976
IOP(mmhg)	12.13±2.70	12.30±2.78	12.33±2.39	0.952

NPDR: Non-proliferative diabetic retinopathy; PDR: Proliferative diabetic retinopathy; IOP: Intraocular pressure. Continuous data are presented as mean ± standard deviation.

Table 2. Distribution of specular microscopy findings by groups

	Control Group (n=30)	NPDR Group (n=30)	PDR Group (n=30)	p value
ct	532.16±28.01	543.40±41.75	554.06±40.04	0.079
cd	2768.36±230.22	2664.06±251.53	2462.60±348.59[a,b]	<0,001
cv	27.53±3.47	29.86±3.94	33.03±4.46[a,b]	<0,001
hex	69.73±4.25	67.03±4.53	63.50±4.76[a,b]	<0,001

NPDR: Non-proliferative diabetic retinopathy; PDR: Proliferative diabetic retinopathy; SD: Standard deviation; ct: corneal thickness (μ); cd: the cell density in the corneal endothelium (cell/mm2); cv: coefficient of variation (the cell area standard deviation/mean cell area μm2); hex: percentage of hexagonal cells (%).

Discussion

In our study, when we compared the control group, which consisted of type 2 DM patients without any ocular findings, with DM patients with NPDR, no significant difference was found in terms of corneal endothelial parameters. A significant difference was found in endothelial cell density (CD), hexagonal cell ratio (HEX) and coefficient of variation (CV) between PDR and both the control and NPDR groups. However, no significant difference was found between the three groups in terms of CT. In DM, pathologies such as corneal edema, delayed corneal wound healing, decreased corneal sensitivity, neurotrophic ulcer, Descemet's membrane wrinkles, corneal endothelial morphology and dysfunction can be observed [13]. Similar to our findings with PDR patients, Sabanci et al. compared non-diabetic and diabetic patients and found that corneal thickness was higher in diabetic patients [14]. Studies conducted by Ermiş, Özdamar, and Lee also reported increased corneal thickness in diabetic patients [15, 16]. It is thought that diabetes causes damage to the corneal endothelium, and this damage causes fluid collection in the cornea by disrupting the corneal hydration balance [17]. Another study suggested that there might be changes in corneal thickness due to inadequate barrier and pump function in the corneal endothelium in DM [18]. Lee et al.'s study compared the corneal morphology of diabetic patients with that of the healthy control group, and a decrease in HEX and CD and an increase in CV were found in the diabetes group [15].

Although it is reported in the literature that the increase in corneal thickness in diabetic patients is due to corneal hydration, the effect of hyperglycemia on the biomechanical properties of collagen has also been implicated. Hyperglycemia accelerates the non-enzymatic glycosylation of biological macromolecules. Glycosylation of corneal collagens causes formation of irreversible cross-links between corneal collagens, and it is thought that this may contribute to the increase in corneal thickness and corneal stiffness [19].

It has been reported that corneal endothelial cell density and hexagonal cell percentage are decreased, while the coefficient of variation is increased in patients with type 2 DM compared to the healthy control group [20]. We obtained similar results in diabetic patients with PDR. On the other hand, Arıcı et al. reported an increase only in CT values in diabetic patients compared to the control group, with no significant difference in other parameters [21].

Conclusion

In conclusion, we found that corneal endothelial parameters deteriorate when diabetes reaches the PDR stage. This situation can lead to both an increase in the susceptibility to corneal diseases and healing problems after cataract surgery in patients with PDR. For this reason, we think that it would be very beneficial to prevent disease progression by strict glucose regulation in type 2 DM patients.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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